(c) screening said population of bi-ligands for binding to an enzyme in said enzyme family;

(d) identifying a bi-ligand that binds to and has specificity for said enzyme; and

(e) repeating steps (c) and (d) to identify a bi-ligand that binds to and has specificity for a second enzyme in said enzyme family.

REMARKS

Claims 9, 11-14 and 37 are under examination. Claims 9, 11-14 and 37 have been amended. New claims 38-48 have been added. Support for the amendments and new claims can be found throughout the specification and the claims as filed. In particular, support for the amendment to claims 9, 11-14 and 37 to recite "enzyme" can be found, for example, on page 11, lines 6-13. Support for the amendment to claim 9 is also supported, for example, on page 8, lines 29-31; page 13, line 32, to page 14, line 2; page 15, lines 1-13; and page 31, lines 23-33, which indicates that a common ligand can be a cofactor or mimic thereof and that a specificity site can be a substrate binding site. Support for new claim 38 can be found in original claim 9, 10 and 11. Support for new claims 41 and 44 can be found in original claims 9, 10 and 12. Support for new claims 39, 40, 42, 43, 45 and 46 can be found in original claims 13 and 14. Support for new claims 47 and 48 can be found, for example, in original claims 9 and 10; on page 8, lines 29-31; page 11, lines 6-13;

page 13, line 32, to page 14, line 2; page 15, lines 1-13; and page 31, lines 23-33. Further support for new claim 47 can be found, for example, on page 32, lines 26-30, which indicates that a common ligand that binds to a conserved site competes for cofactor (natural common ligand) binding. Further support for new claim 48 can be found, for example, on page 10, line 32, to page 11, line 13; and page 12, line 31, to page 13, line 23, which indicates that a receptor family is two or more receptors, that a receptor can be an enzyme, and that an enzyme family binds the same cofactor (natural common ligand). Accordingly, these amendments and new claims do not raise an issue of new matter and entry thereof is respectfully requested.

Applicant has set forth the amendment to the claims in clean form above and in Appendix A, with marked up amendments indicated with brackets and underlining. Entry of the proposed amendments is respectfully submitted to be proper because the amendments are believed to place the claims in condition for allowance.

Applicant appreciates Examiner Baker's time and helpful discussion with Applicant's representatives in the interview on July 23, 2002. Applicant also appreciates Examiner Baker's consideration of proposed draft claim amendments and indication that such amendments would likely overcome the rejections under 35 U.S.C. § 112.

Rejections Under 35 U.S.C. § 112, First Paragraph

The rejection of claims 9, 11-14 and 37 under 35 U.S.C. § 112, first paragraph, as allegedly lacking description in the specification to reasonably convey to one skilled in the art that Applicant was in possession of the claimed invention at the time the application was filed is respectfully traversed. Applicants maintain, for the reasons of record set forth in the response mailed on February 25, 2002, that the specification provides sufficient description and guidance for the terms recited in the claims. Nevertheless, to further prosecution, claim 9 has been amended. The amendment of claim 9 is essentially the same as that provided in draft form to Examiner Baker and indicated in the Interview Summary as likely overcoming the rejections under 35 U.S.C. § 112. Applicant submits that the specification provides sufficient description and guidance to convey to one skilled in the art that Applicant was in possession of the claimed method at the time the application was filed. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

With respect to new claims 38-46, claims 38, 41 and 44 recite substantially the same language as amended claim 9 but are directed to a dehydrogenase enzyme family (claims 38-40), an enzyme family that binds nicotinamide adenine dinucleotide (claims 41-43), and an enzyme family that binds nicotinamide adenine dinucleotide phosphate (claims 44-46). Accordingly, in view of the remarks above and Examiner Baker's indication that such language would likely overcome rejections under 35 U.S.C.

§ 112, Applicant respectfully submits that the specification provides sufficient description and guidance for new claims 38-46. Similarly, Applicant respectfully submits that the specification provides sufficient description and guidance for new claims 47 and 48.

The rejection of claims 9, 11-14 and 37 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement is respectfully traversed. Applicants maintain, for the reasons of record set forth in the response mailed on February 25, 2002, that the specification provides sufficient description and guidance to enable the claimed methods. Nevertheless, to further prosecution, claim 9 has been amended. The amendment of claim 9 is essentially the same as that provided in draft form to Examiner Baker and indicated in the Interview Summary as likely overcoming the rejections under 35 U.S.C. § 112. Applicant submits that the specification provides sufficient description and guidance to enable the claimed methods. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

With respect to new claims 38-46, claims 38, 41 and 44 recite substantially the same language as amended claim 9 but are directed to a dehydrogenase enzyme family (claims 38-40), an enzyme family that binds nicotinamide adenine dinucleotide (claims 41-43), and an enzyme family that binds nicotinamide adenine dinucleotide phosphate (claims 44-46). Accordingly, in view of the remarks above and Examiner Baker's indication that such language would likely overcome rejections under 35 U.S.C. § 112, Applicant respectfully submits that the specification

provides sufficient description and guidance to enable new claims 38-46. Similarly, Applicant respectfully submits that the specification provides sufficient description and guidance to enable new claims 47 and 48.

Rejection Under 35 U.S.C. § 103

The rejection of claims 9, 11-14 and 37 as allegedly obvious over He et al., Bioorg. Med. Chem. Lett. 4:2845-2850 (1994), is respectfully traversed. Applicant submits that the claimed methods are unobvious over He et al.

Applicant respectfully submits that at least two of the requirements to establish a *prima facie* case of obviousness have not been met. First, to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974).

> All words in a claim must be considered in judging the patentability of that claim against the prior art.

In re Wilson, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970) (emphasis added). In contrast to the claimed invention, He et al. does not teach or suggest a method of identifying a population of bi-ligands containing a bi-ligand that binds to and has specificity for a first receptor and a bi-ligand that binds to and has specificity for a second receptor. In this regard, the specification teaches that a

"ligand exhibiting specificity for a receptor in a receptor family differentially binds to a particular receptor, which is measurably higher than the binding of the ligand to at least one other receptor in the same family" (page 45, lines 26-30). In particular with regard to He et al., Table 1 (page 2848) clearly indicates that the compounds have specificity, at best, for only one receptor, protein kinase C (PKC). As illustrated in Exhibit 2 attached with the previous response mailed February 25, 2002, the compounds only exhibited specificity, that is, measurably higher binding, for PKC, but none exhibited specificity for "a second enzyme in said enzyme family." Furthermore, the Office Action acknowledges on page 15, second paragraph, that He et al. lacks the teaching of identifying ligands that have specificity for a second and/or third receptor in the receptor family. Therefore, Applicant submits that He et al. does not teach or suggest all of the claim limitations of the claimed method.

Furthermore, to establish a *prima facie* case of obviousness, there must be motivation to modify the prior art reference to produce the claimed invention (MPEP § 2143.01). Applicant respectfully submits that no such motivation exists in He et al. He et al. describes compounds that are inhibitors of protein kinase C (PKC) and, at best, may provide motivation to identify inhibitors of PKC. However, He et al. provides no motivation to identify a bi-ligand that binds to and has specificity for protein kinase A (PKA), the other kinase analyzed in He et al. for the purpose of showing the specificity of compounds for PKC, let alone any other kinase family member. Therefore, He et al. provides no motivation to identify an

inhibitor for anything other than PKC. Accordingly, He et al. provides no motivation for the claimed method of identifying a population of bi-ligands containing a bi-ligand having specificity for an enzyme and a second bi-ligand having specificity for a second enzyme in the same enzyme family and therefore cannot be considered to render the claims obvious.

Applicant respectfully disagrees with the assertion on page 15, paragraph bridging pages 15-16, that the claims would have been obvious in view of the teachings of He et al. based on the fact that optimization of process steps, especially with respect to ordering, is within the routine skill in the art. The claimed methods are not mere optimization or re-ordering of the description in He et al., which at best may suggest optimization for identifying inhibitors of PKC. The claimed methods are directed to identifying at least two bi-ligands having specificity for two different members of an enzyme family, which requires more than any of the teachings or suggestions in He et al. Furthermore, in regard to the statement in the Office Action that "mere duplication of parts has no patentable significance unless a new and unexpected result is produced," the claimed methods are not merely a duplication of the parts of He et al. because such a duplication, at best, would provide additional inhibitors for PKC but no motivation to identify bi-ligands having specificity for any other kinase family member. Accordingly, based on the teachings in He et al., the identification of an inhibitor for any kinase other than PKC would be an unexpected result and therefore would be considered unobvious over He et al.

In summary, Applicant respectfully submits that He et al. does not teach or suggest each and every element of Applicant's claimed method nor does He et al. provide any motivation to identify a population of bi-ligands containing bi-ligands having specificity for two different members of an enzyme family. Absent such a teaching or suggestion, Applicant respectfully submits that the claimed methods are unobvious over He et al. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

With regard to the new claims, Applicant points out that claims 38-43 are directed to the elected species of dehydrogenase and nicotinamide adenine dinucleotide. Claims 44-46 are directed to nicotinamide adenine dinucleotide phosphate, which Applicant requested be examined with the elected species (see Response mailed August 30, 2001). Applicant also points out the indication in the Office Action mailed November 23, 2001, that the specifically elected species was searched and not found in the prior art (page 4, paragraph 9). Applicant further points out that He et al. does not teach or suggest the claimed methods of identifying a population of bi-ligands to a dehydrogenase (claims 38-40), an enzyme family that binds nicotinamide adenine dinucleotide (claims 41-43) or an enzyme family that binds nicotinamide adenine dinucleotide phosphate (claims 44-46). Absent such a teaching or suggestion, the claimed methods are unobvious over He et al.

CONCLUSION

In light of the amendments and remarks herein, Applicant submits that the claims are now in condition for allowance and respectfully requests a notice to this effect. The Examiner is invited to call the undersigned agent or Cathryn Campbell if there are any questions.

Respectfully submitted,

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Date

Deborah L. Cadena
Registration No. 44,048
Telephone No.: (858) 535-9001
Facsimile No.: (858) 535-8949

CAMPBELL & FLORES LLP
4370 La Jolla Village Drive
Suite 700
San Diego, California 92122
USPTO CUSTOMER NO. 23601

Inventor: Daniel S. Sem
Serial No.: 09/765,696
Filed: January 19, 2001

APPENDIX A

In the claims:

9. (Twice amended) A method for identifying a population of bi-ligands to **[receptors]** **enzymes** in **[a receptor]** **an enzyme** family, comprising

(a) attaching **[an expansion]** **a** linker to a common ligand, wherein said common ligand **[binds to a cofactor binding site and]** **is a cofactor or mimic thereof and** wherein said **[expansion]** linker has sufficient length and orientation to direct a second ligand to a **[specificity]** **substrate binding** site of **[a receptor]** **an enzyme** in said **[receptor]** **enzyme** family, to form a module**[, wherein said receptor is an enzyme]**;

(b) generating a population of bi-ligands, wherein said bi-ligand comprises said module and a second ligand linked by said **[expansion]** linker;

(c) screening said population of bi-ligands for binding to **[a receptor]** **an enzyme** in said **[receptor]** **enzyme** family;

(d) identifying a bi-ligand that binds to and has specificity for said **[receptor]** **enzyme**; and

(e) repeating steps (c) and (d) to identify a bi-ligand that binds to and has specificity for a second **[receptor]** **enzyme** in said **[receptor]** **enzyme** family.

11. (Twice amended) The method of claim 9, wherein said **[receptor]** **enzyme** in said **[receptor]** **enzyme** family is an enzyme selected from the group consisting of a kinase, dehydrogenase, oxidoreductase, GTPase, carboxyl transferase, acyl transferase, decarboxylase, transaminase, racemase, methyl transferase, formyl transferase, and α-ketodecarboxylase.

12. (Twice amended) The method of claim 9, wherein said **[receptor]** **enzyme** family binds a cofactor selected from the group consisting of nicotinamide adenine dinucleotide, nicotinamide adenine dinucleotide phosphate, thiamine pyrophosphate, flavin adenine dinucleotide, flavin mononucleotide, pyridoxal phosphate, coenzyme A, tetrahydrofolate, adenosine triphosphate, guanosine triphosphate and S-adenosyl methionine.

13. (Amended) The method of claim 9, wherein said **[expansion]** linker has approximate C2 symmetry.

14. (Amended) The method of claim 13, wherein said **[expansion]** linker has perfect C2 symmetry.

37. (Amended) The method of claim 9, wherein steps (c) and (d) are repeated to identify a bi-ligand that binds to

and has specificity for a third **[receptor]** **enzyme** in said **[receptor]** **enzyme** family.